

# Respiratory dialysis: Reduction in dependence on mechanical ventilation by venovenous extracorporeal CO<sub>2</sub> removal\*

Andriy I. Batchinsky, MD; Bryan S. Jordan, RN, MSN; Dara Regn, MD; Corina Necsoiu, MD; William J. Federspiel, PhD; Michael J. Morris, MD; Leopoldo C. Cancio, MD

**Objectives:** Mechanical ventilation is injurious to the lung. Use of lung-protective strategies may complicate patient management, motivating a search for better lung-replacement approaches. We investigated the ability of a novel extracorporeal venovenous CO<sub>2</sub> removal device to reduce minute ventilation while maintaining normocarbida.

**Design:** Prospective animal study.

**Setting:** Government laboratory animal intensive care unit.

**Subjects:** Seven sedated swine.

**Interventions:** Tracheostomy, volume-controlled mechanical ventilation, and 72 hrs of round-the-clock intensive care unit care. A 15-F dual-lumen catheter was inserted in the external jugular vein and connected to the Hemolung, an extracorporeal pump-driven venovenous CO<sub>2</sub> removal device. Minute ventilation was reduced, and normocarbida (Paco<sub>2</sub> 35–45 mm Hg) maintained. Heparinization was maintained at an activated clotting time of 150–180 secs.

**Measurements and Main Results:** Minute ventilation (L/min), CO<sub>2</sub> removal by Hemolung (mL/min), Hemolung blood flow, O<sub>2</sub>

consumption (mL/min), CO<sub>2</sub> production by the lung (mL/min), Paco<sub>2</sub>, and plasma-free hemoglobin (g/dL) were measured at baseline (where applicable), 2 hrs after device insertion, and every 6 hrs thereafter. Minute ventilation was reduced from 5.6 L/min at baseline to 2.6 L/min 2 hrs after device insertion and was maintained at 3 L/min until the end of the study. CO<sub>2</sub> removal by Hemolung remained steady over 72 hrs, averaging 72 ± 1.2 mL/min at blood flows of 447 ± 5 mL/min. After insertion, O<sub>2</sub> consumption did not change; CO<sub>2</sub> production by the lung decreased by 50% and stayed at that level ( $p < .001$ ). As the arterial PCO<sub>2</sub> rose or fell, so did CO<sub>2</sub> removal by Hemolung. Plasma-free hemoglobin did not change.

**Conclusions:** Venovenous CO<sub>2</sub> removal enabled a 50% reduction in minute ventilation while maintaining normocarbida and may be an effective lung-protective adjunct to mechanical ventilation. (Crit Care Med 2011; 39:1382–1387)

**KEY WORDS:** lung-protective ventilation; mechanical ventilation; extracorporeal circulation; CO<sub>2</sub> removal; respiratory dialysis; swine

Acute respiratory distress syndrome (ARDS) has a 30%–50% mortality, affects about 150,000 patients per year, and together with chronic lung failure causes one in every seven deaths in the United States (1). Acute lung injury and ARDS are also significant combat casualty care problems stemming from trauma and resuscitation (2, 3), smoke inhalation and burns (4), pulmonary contusion (5), chemical weapons such as mustard agent (6), and blast injury

(7). Toxic industrial chemicals such as chlorine can also lead to ARDS (8) and have been used with improvised explosive devices in a recent conflict (9). Civilian events such as the H1N1 pandemic have the potential to overwhelm the available pool of mechanical ventilators, thus signifying the need for alternative lung support therapies (10).

Although it is the mainstay of current acute lung injury/ARDS therapy, mechanical ventilation is itself injurious, causing

ventilator-induced lung injury (11–16). A recent retrospective study conducted by Wunsch et al (17) using data from six U.S. states found that mechanical ventilation is associated with a high (34.5%) in-hospital mortality rate. Low-tidal-volume lung-protective strategies in ARDS decreased inflammatory mediator levels (12, 15), end-organ dysfunction (15, 18) and mortality (15). Consequences of low-tidal-volume ventilation, however, may include cardiovascular instability, use of high Fio<sub>2</sub>, hypoventilation, alveolar derecruitment, hypercarbia, and acidosis and have led to a search for other lung-protective approaches (1). In addition, the low-tidal-volume strategy, although accepted as a standard of care for ARDS, has in clinical practice been implemented in a variable fashion (19–24).

An alternate approach to treating acute respiratory insufficiency, for avoiding ventilator-induced lung injury, and for achieving “lung rest,” is to perform gas exchange *via* an extracorporeal device (25–31). Such “respiratory dialysis,” arguably, may make it possible to avoid mechanical ventilation altogether in se-

## \*See also p. 1576.

From the U.S. Army Institute of Surgical Research (AIB, BSJ, CN, LCC) and Pulmonary and Critical Care Service (DR, MJM), Brooke Army Medical Center, Fort Sam Houston, San Antonio, TX; and McGowan Institute for Regenerative Medicine (WJF), University of Pittsburgh, Pittsburgh, PA.

Supported, in part, by the Combat Critical Care Engineering Task Area, U.S. Army Institute of Surgical Research.

Presented, in part, at the 75th Annual Meeting of the American College of Chest Physicians, San Diego, CA, November 4, 2009; recipient of a Top Young Investigator award.

Dr. Batchinsky conducted previous research involving the Hemolung device, during which travel and lodging were funded by the device manufacturer. He has nothing

to disclose as pertinent to the work presented in this manuscript. Dr. Federspiel is cofounder of ALung Technologies, manufacturer of the Hemolung device; holds equity interest, stock ownership, and options in ALung Technologies; and has a pending patent from ALung Technologies. The remaining authors have not disclosed any potential conflicts of interest.

The opinions or assertions contained herein are the private views of the authors, and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

For information regarding this article, E-mail: andriy.batchinsky@amedd.army.mil

Copyright © 2011 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins

DOI: 10.1097/CCM.0b013e31820eda45

Report Documentation Page				Form Approved OMB No. 0704-0188	
Public reporting burden for the collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to a penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number.					
1. REPORT DATE <b>01 JUN 2011</b>		2. REPORT TYPE <b>N/A</b>		3. DATES COVERED <b>-</b>	
4. TITLE AND SUBTITLE <b>Respiratory dialysis: reduction in dependence on mechanical ventilation by venovenous extracorporeal CO2 removal</b>				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) <b>Batchinsky A. I., Jordan B. S., Regn D., Necsoiu C., Federspiel W. J., Morris M. J., Cancio L. C.,</b>				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) <b>United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX</b>				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION/AVAILABILITY STATEMENT <b>Approved for public release, distribution unlimited</b>					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT <b>UU</b>	18. NUMBER OF PAGES <b>6</b>	19a. NAME OF RESPONSIBLE PERSON
a. REPORT <b>unclassified</b>	b. ABSTRACT <b>unclassified</b>	c. THIS PAGE <b>unclassified</b>			

lected patients (32). Extracorporeal membrane oxygenation (ECMO) has, to date, been too costly for routine use as a lung rest strategy in adult ARDS patients, although calls for revisiting this technology are emerging (33). Zwischenberger and colleagues (27, 28, 34, 35) developed a less invasive arteriovenous CO<sub>2</sub> removal (AVCO<sub>2</sub>R) system that improved survival in animal studies (27, 28, 34) and has been used safely in clinical studies (35). AVCO<sub>2</sub>R requires an adequate cardiac output and blood pressure as well as separate arterial catheterization, which may lead to limb ischemia (36).

The purpose of the current study was to investigate the potential of a new motor-driven extracorporeal venovenous CO<sub>2</sub> removal device (V<sub>2</sub>CO<sub>2</sub>R) that allows for CO<sub>2</sub> removal at relatively low blood flow rates (400–600 mL/min) (Hemolung, ALung Technologies, Pittsburgh, PA). This technology has high gas exchange efficiency per relatively small membrane surface area (0.59 m<sup>2</sup>). The invasiveness of this device is reduced by use of a dual-lumen catheter and a single-stick venous cannulation, comparable to catheterization for dialysis. Hemolung utilizes a computer-controlled pump, which allows for use in low cardiac output states. In this first report involving the Hemolung, we tested its ability to reduce the need for ventilatory requirements in healthy mechanically ventilated swine over 72 hrs. We hypothesized that Hemolung permits a significant reduction in minute ventilation while maintaining normocarbica and thus could have potential as an adjunct to mechanical ventilation.

## MATERIALS AND METHODS

This study was approved by the U.S. Army Institute of Surgical Research Animal Care and Use Committee and was carried out in accordance with the guidelines set forth by the Animal Welfare Act, other federal statutes and regulations, and the 1996 *Guide for the Care and Use of Laboratory Animals* of the National Research Council.

**Animal Preparation.** Seven female Yorkshire pigs weighing 54.2 kg ± 0.8 SEM were fasted for 24 hrs, induced with isoflurane (2–4 volume %) via mask, and intubated. Next, total intravenous anesthesia (ketamine, 200–500 µg/kg/min; and midazolam, 10–20 mg/hr) was started through an ear vein, and femoral arterial and venous catheters were aseptically placed for blood pressure monitoring, intravenous access, and sample collection. The animals were volume-control ventilated using a Siemens Servo 300A ventilator (Siemens-Elerna, Göteborg, Sweden) with room air at a tidal volume (V<sub>T</sub>)

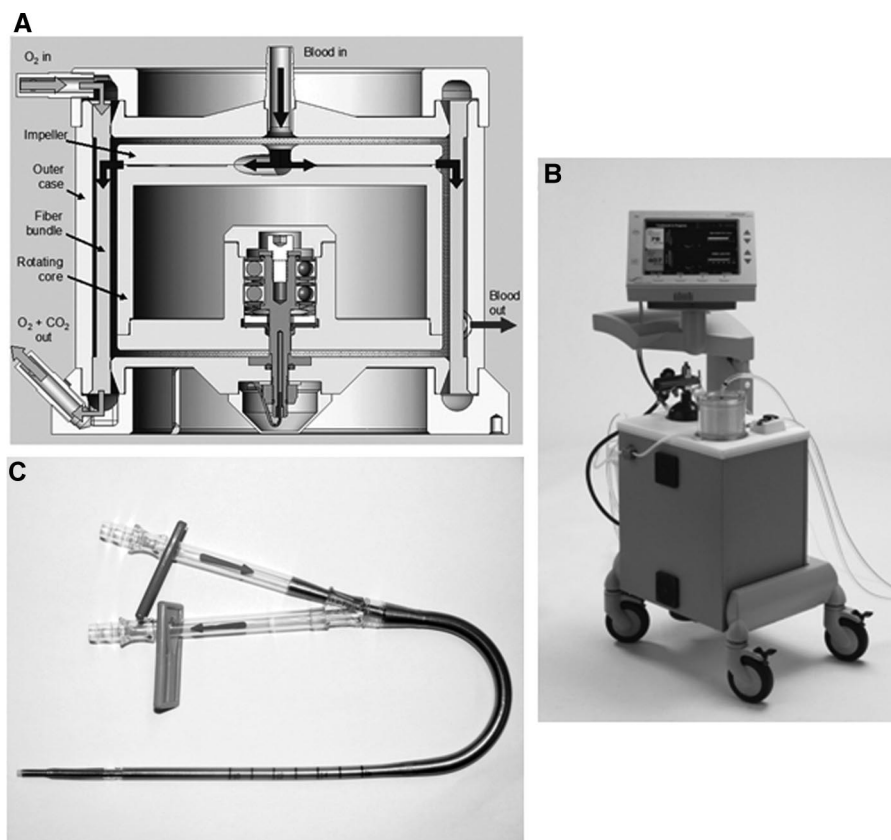


Figure 1. A, Hemolung unit. B, Controller. C, Dual-lumen catheter.

setting of 12 mL/kg and respiratory rate of 8–9 breaths per minute. (This baseline V<sub>T</sub> setting is standard practice in this animal facility and was not intended to conform with current guidelines for low-tidal-volume ventilation in adults with ARDS [15]). The respiratory rate was adjusted at baseline to maintain normocarbica (Paco<sub>2</sub> 35–45 mm Hg). Each animal received a maintenance rate of lactated Ringer's solution to maintain urine output at 0.5–1 mL/kg/hr.

**Hemolung Description and Insertion.** The Hemolung system consists of a unit in which gas exchange takes place (Fig. 1A) and an integrated control console (Fig. 1B). The system is interfaced with the patient through a custom dual-lumen 15-F catheter similar to a dialysis catheter. The catheter is designed to offer low flow resistance and superior kink resistance compared to off-the-shelf dialysis catheters (Fig. 1C). The Hemolung pump withdraws venous blood from the superior vena cava, which after CO<sub>2</sub> removal is reinfused into the right atrium through the distal openings. Inside the Hemolung unit, blood flows centrally into a rotating core, is radially pumped through a stationary annular fiber bundle, and returns to the patient via an outlet port (Fig. 1A). Unlike conventional passive oxygenators, the core uses a motor-driven rotational motion to increase gas exchange efficiency. This motion increases the amount of CO<sub>2</sub> removed relative to the surface area (0.59 m<sup>2</sup>) of the fiber bundles. This increased effi-

ciency permits blood-flow rates comparable to those used in dialysis (300–600 mL/min).

After 1 hr of baseline stabilization of the animals, the Hemolung unit was primed with 300 mL of normal saline containing 5000 units of heparin. The right jugular vein was aseptically exposed via a cut-down. After a 20-u/kg intravenous bolus of heparin, each animal underwent placement of the 15-F catheter through the external jugular vein. The catheter was positioned so that the proximal set of openings was situated in the superior vena cava and the distal tip (with another set of openings) was placed in the right atrium. Upon catheter placement, plastic tubing provided by the manufacturer was immediately connected to each of the two ports of the catheter using the wet-to-wet technique, and the Hemolung unit was started. Placement of the catheter was confirmed via fluoroscopy. The rationale for device insertion in the superior vena cava/right atrium junction was to achieve optimal mixing of the returned "ventilated" blood with systemic blood and to ensure maximal separation of the inflow (into the proximal set of catheter holes) and the outflow (from the distal set of holes). This was based on manufacturer recommendations.

After device insertion, the ventilator settings were reduced according to an algorithm to test the CO<sub>2</sub> removal capacity of the Hemolung. The algorithm did not pursue de-

Table 1. Ventilatory data, blood gas data, and key Hemolung parameters

Variable	Value at					<i>p</i>			
	BL	2 hrs	24 hrs	48 hrs	72 hrs	BL vs. 2 hrs	BL vs. 24 hrs	BL vs. 48 hrs	BL vs. 72 hrs
Minute ventilation, L/min	5.6 ± 0.3	2.6 ± 0.3 <sup>a</sup>	3.0 ± 0.1 <sup>a</sup>	3.1 ± 0.2 <sup>a</sup>	3.3 ± 0.2 <sup>a</sup>	.02	.0004	.0003	.0002
Respiratory rate, bpm	9	5 <sup>a</sup>	5 <sup>a</sup>	5 <sup>a</sup>	5 <sup>a</sup>	.0002	.0004	.001	.003
Tidal volume, mL	650 ± 14	556 ± 24	576 ± 9	574 ± 15	578 ± 15	.087	.084	.16	.18
Pao <sub>2</sub> , mm Hg	96 ± 2	77 ± 5 <sup>a</sup>	103 ± 8	97 ± 16	112 ± 8	.04	.94	.55	.08
Paco <sub>2</sub> , mm Hg	39 ± 0.8	43 ± 2.2	42 ± 1.0	44 ± 1.2 <sup>a</sup>	46 ± 5.8 <sup>a</sup>	.52	.08	.01	.0003
pH	7.46 ± 0.0	7.41 ± 0.0	7.47 ± 0.0	7.45 ± 0.0	7.44 ± 0.0	.14	.98	1.0	.99
CO <sub>2</sub> removal by the Hemolung device, mL/min	n/a	76 ± 3.0	73 ± 1.2	69 ± 2.7	65 ± 2.6 <sup>a</sup>	n/a	.62 <sup>b</sup>	.17 <sup>b</sup>	.03 <sup>b</sup>
Blood flow through the Hemolung device, mL/min	n/a	422 ± 11	471 ± 24	445 ± 29	431 ± 21	n/a	.42 <sup>b</sup>	.77 <sup>b</sup>	.67 <sup>b</sup>

BL, baseline.

<sup>a</sup>Significant difference vs. baseline at *p* < .05; <sup>b</sup>comparison of time point data to 2-hr postinsertion time point. All data are means ± SEM. Statistics by one-way analysis of variance with repeated measures and adjustment to multiple comparisons.

creases in  $V_T$  as the primary mechanism for reducing minute ventilation as recommended for ARDS patients (12, 15, 18), because this study focused on assessing the Hemolung's CO<sub>2</sub> removal capacity, without regard to how the decrease in minute ventilation was achieved. First, respiratory rate was reduced to the minimum setting allowed by the ventilator (5 breaths per minute) and kept there unless hypercarbia above the target level (Paco<sub>2</sub> 35–45 mm Hg) developed. Further decreases in minute ventilation were sought via reduction in  $V_T$  in 2 mL/kg steps as verified by blood gas analysis (Roche, CO Bas B 221, Indianapolis, IN). CO<sub>2</sub> removal by the Hemolung was assessed by comparing data from the time point immediately after device insertion (hour 2) to data from the subsequent time points in the study. After device insertion, animals were maintained for 72 hrs with round-the-clock care in an animal intensive care unit.

**Measurements.** Heparin was given continuously during the study and assessed by the activated clotting time (in seconds) using a Hemochron Jr Signature Microcoagulation System (International Technidyne, Piscataway, NJ). The target level for heparinization was a relatively low activated clotting time of 150–180 secs (37). Heart rate (beats per minute), systolic arterial pressure (mm Hg), minute ventilation ( $V_E$ , L/min), respiratory rate (breaths/minute), and  $V_T$  (mL/min) were recorded. Pulmonary oxygen consumption (mL/min) and CO<sub>2</sub> production (mL/min) were measured using a Deltatrac II metabolic cart (Sensor Medics, Yorba Linda, CA) and were adjusted for body surface area. Hemolung blood flow (L/min), CO<sub>2</sub> removal rate (mL/min) and sweep gas flow (mL/min) were recorded from the Hemolung console. Arterial tension of oxygen (Pao<sub>2</sub>, mm Hg) and CO<sub>2</sub> (Paco<sub>2</sub>, mm Hg) were measured at baseline, 2 hrs after insertion of the Hemolung and every 6 hrs thereafter.

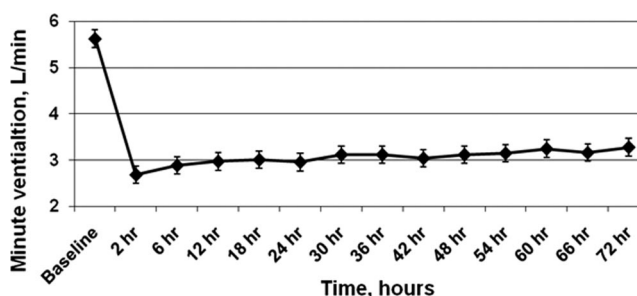


Figure 2. Changes in minute ventilation over time. For statistical significance, see Table 1.

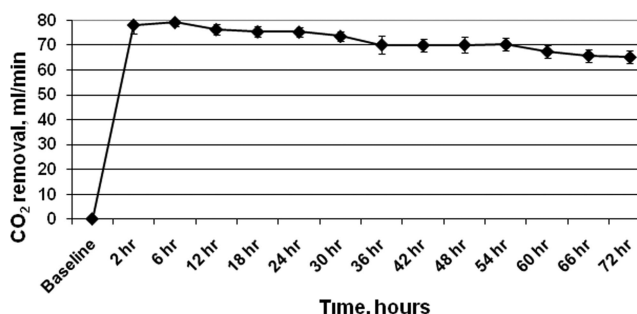


Figure 3. Changes in CO<sub>2</sub> removal over time. For statistical significance, see Table 1.

Plasma-free hemoglobin (g/dL) was determined using spectrophotometry (38).

**Statistical Analysis.** Statistical analysis by one-way analysis of variance with repeated measures and Dunnett's adjustment for multiple comparisons was performed using SAS v. 9.1. (SAS, Cary, NC). The data presented were normally distributed. Significance was accepted at *p* < .05.

## RESULTS

A total of 504 hrs of intensive care unit care were provided in the conduct of this

study.  $V_E$  and respiratory rate decreased 2 hrs after device placement and remained at 50% of baseline values throughout the duration of the study (Table 1, Fig. 2).  $V_T$  was about 75 to 100 mL lower at each time point compared to baseline values, but these changes were not significant. Pao<sub>2</sub> was lower at 2 hrs, whereas Paco<sub>2</sub> was higher at 48 and 72 hrs after insertion when compared to baseline values (Table 1). The pH was unchanged throughout the study. Mean CO<sub>2</sub> removal by Hemolung over the study duration was

Table 2. Hemodynamic and metabolic data

Variable	Value at					<i>p</i>			
	BL	2 hrs	24 hrs	48 hrs	72 hrs	BL vs. 2 hrs	BL vs. 24 hrs	BL vs. 48 hrs	BL vs. 72 hrs
Heart rate, bpm	100 ± 11	86 ± 11	77 ± 6 <sup>a</sup>	89 ± 9	84 ± 6	.23	.02	.49	.89
Systolic arterial pressure, mm Hg	130 ± 8	125 ± 6	117 ± 6	114 ± 11	117 ± 15	.99	.55	.46	.50
Lung O <sub>2</sub> consumption, mL/min	313 ± 37	320 ± 39	259 ± 26	277 ± 33	262 ± 31	.98	.09	.56	.06
Lung CO <sub>2</sub> production, mL/min	262 ± 27	135 ± 15 <sup>a</sup>	141 ± 13 <sup>a</sup>	152 ± 17 <sup>a</sup>	147 ± 18 <sup>a</sup>	.0005	<.0001	<.0001	<.0001
Plasma-free hemoglobin, mg/dL	14.6 ± 2.4	10.5 ± 1.5	17.6 ± 5.8	10.9 ± 1.8	16.6 ± 2.8	.81	.99	.76	.98
Activated clotting time, secs	106 ± 4	186 ± 25	141 ± 24	150 ± 22	135 ± 25	.10	.69	.44	.57

BL, baseline.

<sup>a</sup>Significant difference vs. baseline at *p* < .05. All data are means ± SEM. Statistics by one-way analysis of variance with repeated measures and adjustment to multiple comparisons.

72 ± 1.2 mL/min. It remained not different from the postinsertion time point (hour 2) at all time points, other than at the 72-hr time point when it decreased to a mean of 65 mL/min (Table 1, Fig. 3). Mean blood flow through the Hemolung over the study was 447 ± 5 mL/min and remained steady (Table 1). Revolutions per minute of the motor remained steady in the 1200–1300 range throughout the 72 hrs (data not shown). Sweep gas flow averaged 8.6 L/min throughout the study and was kept constant to avoid the effect of changes on CO<sub>2</sub> removal (data not shown). Heart rate and systolic arterial pressure did not change after placement of the Hemolung unit at any time, except 24 hrs after Hemolung placement when heart rate decreased from 100 to 77 beats/min (Table 2). O<sub>2</sub> consumption did not change, whereas CO<sub>2</sub> production by the lung decreased significantly at all time points after device placement to nearly half of the baseline value (Table 2). Activated clotting time remained unchanged throughout the study. The plasma-free hemoglobin levels remained not different from baseline throughout the duration of the study (Table 2).

## DISCUSSION

This the first report on *in vivo* use of the Hemolung V<sub>2</sub>CO<sub>2</sub>R device. Our aim was to benchmark this technology for its capacity to eliminate CO<sub>2</sub> and to permit a significant reduction in V<sub>E</sub>. The main finding is that during a 72-hr experiment, the Hemolung removed an average of 72 mL/min of CO<sub>2</sub> at 450 mL/min blood flow through the device, and allowed for maintenance of normocarbia in spite of a 50% reduction in V<sub>E</sub>. The Hemolung did not cause hemodynamic instability or erythrocyte destruction, suggesting that it may have a potential in supplementing

mechanical ventilation while permitting the lung to heal (31) or even replacing the ventilator altogether (32).

Artificial lung support systems are medical devices designed to supplement or replace the respiratory function of the natural lung. ECMO was introduced for treatment of neonatal respiratory failure (39). ECMO is currently used in adults only in a few centers, requires highly trained staff, and is considered complicated and costly but effective for selected patients with severe pulmonary failure (10, 40, 41). Alpar, Zwischenberger, and colleagues (27, 28, 34, 42) developed a simpler extracorporeal AVCO<sub>2</sub>R system using a low-resistance ECMO oxygenator for gas exchange and showed that it permitted a reduction in minute ventilation, reduced airway pressure, improved PaO<sub>2</sub>-to-FiO<sub>2</sub> ratio, and improved survival in animal models of ARDS. Another AVCO<sub>2</sub>R device, marketed in Europe as the Interventional Lung Assist device (NovaLung), has also shown promise in the treatment of acute lung failure and as a means of lung rest (29, 30, 36). However, compared to the Hemolung, currently available AVCO<sub>2</sub>R devices require a higher blood flow (500–1500 mL/min), rely on the arteriovenous pressure gradient (which could be difficult in hemodynamically unstable patients), and carry a risk of limb ischemia due to arterial cannulation (36).

Unlike passive oxygenators, which rely on the arteriovenous pressure gradient and require both arterial and venous cannulation for gas exchange (30), the Hemolung uses a single-stick dual-lumen venous cannula and an extracorporeal computer-driven pump. This motor, by increasing blood flow across the fibers, allows for optimized CO<sub>2</sub> elimination for a membrane surface area of only 0.59 m<sup>2</sup>. Increased gas exchange efficiency in the

Hemolung permits use of lower dialysis-level blood flow rates in the 300–750-mL/min range, compared to 500–1500 mL/min in the current AVCO<sub>2</sub>R devices (27, 30, 35, 43, 44). Our study also highlights several other features of the Hemolung when compared to other devices. First, in the present study a 15-F dual-lumen catheter was used, which is smaller than most currently used catheters and which permits for a single-stick venous insertion. Avoidance of arterial cannulation is a benefit of this system as it may lower the risk of lower limb ischemia, hemorrhage, and systemic thromboembolism. Second, Hemolung insertion and function did not lead to hemodynamic changes, as neither heart rate nor blood pressure changed clinically significantly at any time during the experiment. This feature may extend the applicability of this technology to hemodynamically unstable patients. Third, plasma-free hemoglobin did not change, indicating that the extracorporeal circuit did not cause erythrocyte lysis. Fourth, the Hemolung can be operated using only ambient air for sweep gas and CO<sub>2</sub> removal. This may make it amenable for use during transport, while reducing the need for oxygen tanks.

The present study did not pursue the minimal possible dose of heparin required for use with the Hemolung, but the activated clotting time values obtained (150–180 secs) are significantly lower than the systemic heparinization levels traditionally employed with similar technology (37, 43). Future work will explore the feasibility of avoiding systemic heparinization altogether. Cardenas et al (44), for example, recently described a CO<sub>2</sub> removal device in which regional heparinization (i.e., heparinization of the extracorporeal circuit

alone) was sufficient to achieve adequate device performance.

$V_2\text{CO}_2\text{R}$  is a relatively new form of extracorporeal lung support. Cardenas et al (44) used a modified ECMO system, a single-stick dual-lumen catheter, and a pump to perform  $V_2\text{CO}_2\text{R}$  in a manner similar to that used in our study. At comparable blood flows (500 mL/min), it achieved about the same  $\text{CO}_2$  removal that we observed in the present study. By doubling the blood flow to 1000 mL/min and with a 15-L/min sweep gas flow (twice the settings of the present study), they reached a  $\text{CO}_2$  elimination rate of 150 mL/min (44). Recently, a unique  $V_2\text{CO}_2\text{R}$  approach was tested in humans with ARDS, in which a pediatric ECMO system (membrane surface area 0.33  $\text{m}^2$ ) was connected in series with a dialysis circuit (45).  $V_T$  was reduced below the 6-mL/kg ARDSNet recommended target, and the resulting respiratory acidosis was successfully managed via the extracorporeal circuit. The authors concluded that their  $V_2\text{CO}_2\text{R}$  system allowed for safe use of lower-than-customary tidal volumes (45). Taken together, these studies and our experience support the concept that extrapulmonary  $\text{CO}_2$  removal, by permitting a reduction in ventilator settings, can serve as a lung-protective strategy (47).

$\text{CO}_2$  removal rates were steady over the course of our experiment, especially considering the low blood flow rates used. In general,  $\text{CO}_2$  removal is a function of three conditions: 1)  $\text{Paco}_2$ , in that an increase in  $\text{Paco}_2$  leads to an increase in the extracorporeal  $\text{VCO}_2$ ; 2) sweep gas flow rate (regulated by the user); and 3) blood flow through the device (a function of the catheter size and the device revolutions per minute). Because higher revolutions per minute may lead to hemolysis, more efficient gas exchange at lower rates is desirable. Device insertion was associated with a decreased (but still normal)  $\text{Pao}_2$  at 2 hrs. This may represent the decrease in  $V_E$ , and/or transient changes in ventilation/perfusion matching in the lung.

In this study in animals with normal lungs, we did not attempt to duplicate ARDSNet low-tidal-volume recommendations, and we achieved decreases in  $V_E$  primarily by decreasing the respiratory rate. More work will be required to characterize the performance of this system in ARDS models.

The current study was designed to use the Hemolung in conjunction with mechanical ventilation to achieve a “nor-

mal” blood gas, defined as arterial oxygen saturation above 92% and  $\text{Paco}_2$  of 35–45 mm Hg. By contrast, in the clinical care of patients with acute lung injury/ARDS, permissive hypercapnia is employed as long as the pH is within safe limits. The absence of hypercapnia in this study limited our ability to explore the maximal rate of  $\text{CO}_2$  elimination. In bench studies by the Hemolung developers (46), the  $\text{CO}_2$  removal by Hemolung of a prototype was estimated to be 250 mL/min/ $\text{m}^2$  at 1500 rpm, assuming a membrane with a 0.4  $\text{m}^2$  surface area. We expect to challenge the Hemolung for its maximal  $\text{CO}_2$  removal by Hemolung in follow-up studies involving animals with ARDS. Those studies will also pursue a less invasive femoral placement of the catheter as well as quantification of the oxygenation capacity by the Hemolung, which was not addressed in this experiment.

## CONCLUSIONS

In summary, use of the Hemolung for  $V_2\text{CO}_2\text{R}$  in an uninjured porcine model allowed a significant and sustained reduction in  $V_E$  while maintaining normocarbida. The system performed about 50% of ventilatory function via percutaneous venous cannulation with a dual-lumen catheter similar to a dialysis catheter. Gas exchange efficiency was maintained for 72 hrs at low flow rates. No pronounced hemodynamic effects upon insertion and during operation were observed. Overt erythrocyte destruction was absent. Because of its ease of use, Hemolung may also make it possible to more rapidly initiate extracorporeal lung support in emergency departments and community intensive care units.  $V_2\text{CO}_2\text{R}$ , a relatively easy-to-employ extracorporeal lung support technology, may reduce levels of injurious mechanical ventilation and may even permit some patients to avoid mechanical ventilation entirely.

## ACKNOWLEDGMENTS

We dedicate this work to Dr. Brack Hattler and his family. Dr. Hattler passed away in 2008. He was a pioneer of artificial lung support research and continues to be an inspiration to generations of physicians and scientists.

We acknowledge the technical assistance of Ms. Otilia Sánchez, a professional writer, in helping to prepare the manuscript.

## REFERENCES

1. Zwischenberger BA, Clemson LA, Zwischenberger JB: Artificial lung: Progress and prototypes. *Expert Rev Med Dev* 2006; 3:485–497
2. Ashbaugh DG, Bigelow DB, Petty TL, et al: Acute respiratory distress in adults. *Lancet* 1967; 2:319–323
3. Simmons RL, Heisterkamp CA III, Collins JA, et al: Acute pulmonary edema in battle casualties. *J Trauma* 1969; 9:760–775
4. Pinkstaff CA, Sturtz DL, Bellamy RF: USS Franklin and the USS Stark—recurrent problems in the prevention and treatment of naval battle casualties. *Mil Med* 1989; 154: 229–233
5. Moseley RV, Doty DB, Pruitt BA Jr: Physiologic changes following chest injury in combat casualties. *Surg Gynecol Obstet* 1969; 129:233–242
6. Freitag L, Firusian N, Stamatis G, et al: The role of bronchoscopy in pulmonary complications due to mustard gas inhalation. *Chest* 1991; 100:1436–1441
7. Grau LW, Smith T: A ‘crushing’ victory: Fuel-air explosives and Grozny 2000. Foreign Military Studies Office Publications, Fort Leavenworth, KS. Available at: <http://fmso.leavenworth.army.mil/documents/fuelair/fuelair.htm>. Accessed February 7, 2011
8. Batchinsky AI, Martini DK, Jordan BS, et al: Acute respiratory distress syndrome secondary to inhalation of chlorine gas in sheep. *J Trauma* 2006; 60:944–956, discussion 956–947
9. Weitz R, Al-Marashi I, Hilal K: Chlorine as a terrorist weapon in Iraq. Issues and viewpoints in the international media. 2007. Available at: [http://www.wmdinsights.com/115/115\\_ME1\\_Chlorine.htm](http://www.wmdinsights.com/115/115_ME1_Chlorine.htm). Accessed February 7, 2011
10. Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators, Davies A, Jones D, et al: Extracorporeal Membrane Oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. *JAMA* 2009; 302:1888–1895
11. Amato MB, Barbas CS, Medeiros DM, et al: Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998; 338:347–354
12. Ranieri VM, Suter PM, Tortorella C, et al: Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 1999; 282:54–61
13. Chiumello D, Pristine G, Slutsky AS: Mechanical ventilation affects local and systemic cytokines in an animal model of acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1999; 160:109–116
14. Slutsky AS: Lung injury caused by mechanical ventilation. *Chest* 1999; 116:9S–15S.
15. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute

- respiratory distress syndrome. *N Engl J Med* 2000; 342:1301–1308
16. Gattinoni L, Protti A, Caironi P, et al: Ventilator-induced lung injury: The anatomical and physiological framework. *Crit Care Med* 2010; 38:S539–S548
  17. Wunsch H, Linde-Zwirble WT, Angus DC, et al: The epidemiology of mechanical ventilation use in the United States. *Crit Care Med* 2010; 38:1947–1953
  18. Ranieri VM, Giunta F, Suter PM, et al: Mechanical ventilation as a mediator of multi-system organ failure in acute respiratory distress syndrome. *JAMA* 2000; 284:43–44
  19. Thompson BT, Hayden D, Matthay MA, et al: Clinicians' approaches to mechanical ventilation in acute lung injury and ARDS. *Chest* 2001; 120:1622–1627
  20. Weinert CR, Gross CR, Marinelli WA: Impact of randomized trial results on acute lung injury ventilator therapy in teaching hospitals. *Am J Respir Crit Care Med* 2003; 167: 1304–1309
  21. Dellinger RP: Positive clinical impact of low tidal volume strategy. *Crit Care Med* 2005; 33:1143–1144
  22. Hager DN, Krishnan JA, Hayden DL, et al: Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. *Am J Respir Crit Care Med* 2005; 172:1241–1245
  23. Checkley W, Brower R, Korpak A, et al: Effects of a clinical trial on mechanical ventilation practices in patients with acute lung injury. *Am J Respir Crit Care Med* 2008; 177:1215–1222
  24. Deans KJ, Minneci PC, Cui X, et al: Mechanical ventilation in ARDS: One size does not fit all. *Crit Care Med* 2005; 33:1141–1143
  25. Alpard SK, Zwischenberger JB: Extracorporeal gas exchange. *Respir Care Clin N Am* 1998; 4:711–738, ix
  26. Alpard SK, Zwischenberger JB: Extracorporeal membrane oxygenation for severe respiratory failure. *Chest Surg Clin N Am* 2002; 12:355–378, vii
  27. Zwischenberger JB, Alpard SK, Tao W, et al: Percutaneous extracorporeal arteriovenous carbon dioxide removal improves survival in respiratory distress syndrome: A prospective randomized outcomes study in adult sheep. *J Thorac Cardiovasc Surg* 2001; 121:542–551
  28. Zwischenberger JB, Wang D, Lick SD, et al: The paracorporeal artificial lung improves 5-day outcomes from lethal smoke/burn-induced acute respiratory distress syndrome in sheep. *Ann Thorac Surg* 2002; 74: 1011–1016, discussion 1017–1018
  29. Fischer S, Hoepfer MM, Tomaszek S, et al: Bridge to lung transplantation with the extracorporeal membrane ventilator Novalung in the veno-venous mode: The initial Hannover experience. *ASAIO J* 2007; 53:168–170
  30. Nielsen ND, Kjaergaard B, Koefoed-Nielsen J, et al: Apneic oxygenation combined with extracorporeal arteriovenous carbon dioxide removal provides sufficient gas exchange in experimental lung injury. *ASAIO J* 2008; 54: 401–405
  31. Pesenti A, Patroniti N, Fumagalli R: Carbon dioxide dialysis will save the lung. *Crit Care Med* 2010; 38:S549–S554
  32. Del Sorbo L, Ranieri VM: We do not need mechanical ventilation any more. *Crit Care Med* 2010; 38:S555–S558
  33. Blum J M, Rosenberg AL: It's time to reconsider adult ECMO. *Chest Physician* 2010; 5:9
  34. Schmalstieg FC, Kenney SE, Rudloff HE, et al: Arteriovenous CO<sub>2</sub> removal improves survival compared to high frequency percussive and low tidal volume ventilation in a smoke/burn sheep acute respiratory distress syndrome model. *Ann Surg* 2007; 246:512–521, discussion 521–513
  35. Zwischenberger JB, Conrad SA, Alpard SK, et al: Percutaneous extracorporeal arteriovenous CO<sub>2</sub> removal for severe respiratory failure. *Ann Thorac Surg* 1999; 68:181–187
  36. Bein T, Weber F, Philipp A, et al: A new pumpless extracorporeal interventional lung assist in critical hypoxemia/hypercapnia. *Crit Care Med* 2006; 34:1372–1377
  37. Zwischenberger JB, Vertrees RA, Woodson LC, et al: Percutaneous venovenous perfusion-induced systemic hyperthermia for advanced non-small cell lung cancer: Initial clinical experience. *Ann Thorac Surg* 2001; 72:234–242
  38. Noe DA, Weedn V, Bell WR: Direct spectrophotometry of serum hemoglobin: An Allen correction compared with a three-wave-length polychromatic analysis. *Clin Chem* 1984; 30:627–630
  39. Bartlett RH, Gazzaniga AB, Toomasian J, et al: Extracorporeal membrane oxygenation (ECMO) in neonatal respiratory failure. 100 cases. *Ann Surg* 1986; 204:236–245
  40. Peek GJ, Mugford M, Tiruvoipati R, et al: Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): A multicentre randomised controlled trial. *Lancet* 2009; 374:1351–1363
  41. Gattinoni L, Pesenti A, Mascheroni D, et al: Low-frequency positive-pressure ventilation with extracorporeal CO<sub>2</sub> removal in severe acute respiratory failure. *JAMA* 1986; 256: 881–886
  42. Alpard SK, Zwischenberger JB, Tao W, et al: Reduced ventilator pressure and improved P/F ratio during percutaneous arteriovenous carbon dioxide removal for severe respiratory failure. *Ann Surg* 1999; 230:215–224
  43. Zhou X, Loran DB, Wang D, et al: Seventy-two hour gas exchange performance and hemodynamic properties of NOVALUNG iLA as a gas exchanger for arteriovenous carbon dioxide removal. *Perfusion* 2005; 20:303–308
  44. Cardenas VJ Jr, Miller L, Lynch JE, et al: Percutaneous venovenous CO<sub>2</sub> removal with regional anticoagulation in an ovine model. *ASAIO J* 2006; 52:467–470
  45. Terragni PP, Del Sorbo L, Mascia L, et al: Tidal volume lower than 6 ml/kg enhances lung protection: role of extracorporeal carbon dioxide removal. *Anesthesiology* 2009; 111:826–835
  46. Svitek RC, Frankowski BJ, Federspiel WJ: Evaluation of a pumping assist lung that uses a rotating fiber bundle. *ASAIO J* 2005; 51: 773–780
  47. Kolobow T, Gattinoni L, Tomlinson T, et al: An alternative to breathing. *J Thorac Cardiovasc Surg* 1978; 75:261–266